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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/705,022	Applicant(s) UMLAUF, SCOTT	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-41 is/are pending in the application.

4a) Of the above claim(s) 26-41 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 01 November 2000 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: 5 .

DETAILED ACTION

Non-Final Rejection

Claims 1-25 are pending examination.

Applicants elected Group I (claims 1-25) without traverse in paper no. 11 filed on 4/4/02.

Claims 26-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11.

Specifications/Informalities

The disclosure is objected to because of the following informalities: A line that appears in the specification at page 63, line 21. Clarification is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25 as best understood, are readable on a genus of a promoter **derived** from a gene encoding a co-stimulatory molecule, wherein the genus of a promoter derived from a gene encoding a co-stimulatory molecule is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates production of a genus of a promoter derived from a gene encoding a co-stimulatory molecule. The as-filed specification provides sufficient description of a promoter from a co-stimulatory molecule selected from either a CD80 or a CD86 gene.

However, it is not apparent in the specification or in the prior art as to any other promoter derived from a gene encoding a co-stimulatory molecule or a promoter derived from a gene encoding either a CD80 or CD86 gene. The metes and bounds of the claims cannot be ascertained because of the nature of any promoter derived from a gene encoding a co-stimulatory molecule that might contain sequences derived from either a promoter derived from a gene encoding a co-stimulatory molecule or a promoter derived from a CD80 or CD86 sequence in their respective genomes; what is required is the knowledge in the prior art and/or as to the availability of a representative number of species of biochemical or molecular structure of promoters derived from genes encoding a co-stimulatory molecule or promoters derived from CD80 and CD86 genes, and/or final products of polynucleotide sequences that must exhibit the disclosed biological functions as contemplated by the claims.

Furthermore, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of a promoter derived from a gene encoding a co-stimulatory molecule as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of a

promoter derived from a gene encoding a co-stimulatory molecule that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to the genus of a promoter derived from a gene encoding a co-stimulatory molecule. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming an unspecified genus of a promoter derived from a gene encoding a co-stimulatory molecule that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus a promoter derived from a gene encoding a co-stimulatory molecule that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A polynucleotide sequence comprising either a promoter of a CD80 gene or a CD86 gene operably linked to a nucleotide sequence encoding at least one antigen; 2) The polynucleotide sequence of 1, further comprising another sequence encoding at least one cytokine operably linked to the promoter, 3) A method for eliciting an immune response in a vertebrate subject, the method comprising: (a) providing a nucleotide sequence encoding an antigen operably linked to either a CD80 or a CD86 promoter; and (b) administering the nucleotide sequence to the subject, whereby antigen is expressed in an amount sufficient to elicit an immune response, 4) A method for eliciting an immune response in a vertebrate subject, the method comprising: (a) providing a core carrier particle coated with a nucleotide sequence encoding at least one antigen operably linked to either a promoter of a CD80 gene or CD86 gene; and (b) administering the coated particle to the subject using a particle-mediated transdermal delivery technique, whereby antigen is expressed in an amount sufficient to elicit an immune response, and does not reasonably provide enablement for other claimed embodiments embraced by the breadth of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of a promoter derived from a gene encoding a co-stimulatory molecule), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as

intended, e.g. function in a polynucleotide used for expressing an antigen in a subject in an amount sufficient to elicit an immune response.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The field of the invention lies in producing a polynucleotide sequence comprising a promoter derived from a gene encoding a co-stimulatory molecule and a nucleotide sequence encoding at least one antigen wherein said nucleotide sequence encoding an antigen is operably linked to the promoter and using the sequence in a method of eliciting an immune response in a vertebrate subject.

Furthermore, with respect to making and using a promoter derived from a gene encoding a co-stimulatory molecule, the state of the art teaches that different promoters work with different efficiencies (Manias, 1982, page 405). Manias teaches:

> Comparison of the sequences of a number of different promoters reveals two highly conserved regions. These two regions are thought to be important in determining promoter strength because mutations that decrease the frequency of transcription usually decrease the amount of homology with the conserved sequences. However, other, more moderately conserved regions of promoters may also contribute to promoter strength. Furthermore, the number of nucleotides that separate the conserved sequences is important for efficient promoter function. For example, see Crombrugghe et al. 1971; Stefano and Gralla 1982. These results indicate either that there is an optimal spacing for any individual promoter that is dependent on its particular DNA sequence. page 405.

The experimentation of studying a promoter is further exemplified by Zhang, who teaches isolating and mapping of the gene encoding murine co-stimulatory factor B7-1 promoter (IDS, Zhang et al., Gene Vol. 183, 1996).

The application provides examples for making and using the CD80 promoter (pages 49-63). One example displays that the DNA sequence for the human and mouse CD80 promoter genes were obtained from the GenBank Database and that the CD80 promoters were made by primers obtained from Gibco (page 49). Another example demonstrated an increase in cytotoxic lymphocyte (CTL) response by particle-mediated delivery into the epidermis of non-diseased mice using a CD80 promoter driven HbsAg plasmids after a booster administration following the same protocol used for prime immunization of the mice (page 55). In addition, the specification contemplates that the promoter can be derived from a regulatory sequence which controls transcription of a co-stimulatory molecule for example, a promoter derived from a CD80, CD86, CD40, CD54 gene. Other suitable promoters can be readily determined using methods known in the art (pages 30-32).

As stated above, the claimed invention teaches one skilled in the art how to make and/or use a CD80 or CD86 promoter in the production of an immunogenic composition comprising a polynucleotide sequence comprising a CD80 or CD86 promoter operably linked to at least one nucleotide sequence encoding an antigen. However, in view of the art of record and the lack of sufficient guidance or factual evidence provided by the specification, the claimed invention is not enabled for making and/or using any promoter derived from a gene encoding a co-stimulatory molecule because it is not apparent as how one skilled in the art reasonably extrapolates, without undue experimentation, from using a promoter from a CD80 or CD86 gene to using any promoter derived from a gene encoding a co-stimulatory molecule being sought in the claimed invention to the full scope of the claimed invention that would generate an immune response in a subject comprising biological properties as contemplated by applicant's disclosure. The CD80

and CD86 promoters are well known in the art. However, the structural differences between unspecified promoters derived from a gene encoding a co-stimulatory molecules are not comparable due to the unspecified chemical structures and with the unpredictability in the art of protein-structure prediction, it is not apparent as to how one skilled in the art would be able to determine without undue experimentation what sequences are derived from a gene encoding a co-stimulatory molecule (Ngo et al., *The Protein Folding Problem and Tertiary Structure Prediction*, Birkhauser Boston, 1994, Chapter 14, pp. 491-495). Even if the biological properties contemplated by applicant's disclosure has been shown in cell lines using the CD80 promoter or in the prior art with the CD86 promoter, it is not apparent as to how to make and/or use promoters derived from a gene encoding a co-stimulatory molecule is reasonably extrapolated to the full scope of the claimed invention, encompassing any co-stimulatory molecule given that there is no evidence that the CD80 or CD86 promoter is a general phenomenon, and given the doubts expressed in the art of record.

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed promoters derived from a gene encoding a co-stimulatory molecule generates an immune response other than the CD80 and CD86 promoters, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any of the other promoters as contemplated by the claims, particularly given the unpredictability of deriving promoters from a gene encoding a co-stimulatory molecule and/or the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably

enable the for 1-4 listed above. Given that nucleotide sequence comprising a promoter **derived** from a gene encoding a co-stimulatory molecule operably linked to a sequence encoding at least one antigen, wherein the nucleotide sequence is employed to elicit an immune response in a vertebrate subject was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a promoter derived from a gene encoding a co-stimulatory molecule cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of producing promoters derived from a gene encoding a co-stimulatory molecule.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-3, 9, 11, 14, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The statement in claims 9 and 11, "... **a** polynucleotide according to claim 1" is indefinite because it does not point out which polynucleotide, a polynucleotide according to claim 1 is referring to in either claim. Claim 1 refers to one polynucleotide and the dependent claims refer to more than one polynucleotide. The dependent claim should state "……..**the** polynucleotide according to claim 1".

The term "derived" in claims 1-3, 14, and 20 is a relative term, which renders the claim indefinite. The term "derived" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be

reasonably apprised of the scope of the invention. The disclosure does not define the metes and bounds of the term that embraces the specific term "substantially" (page 16). More specifically, the specification does not define the metes and bounds of the phrase "**substantially** the same basepair sequence as a region of the promoter region of the promoter region of the co-stimulatory molecule" (page 16).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

Claims 1-3, 11, and 14-15 are rejected under 35 U.S.C 103(a) as being unpatentable over Krieg et al. (US Patent No. 6,339,068) taken with Ellis et al. (IDS, Journal of Immunology, Vol. 56, 1996) in further view of either Zhang (IDS, Gene, 1996) or Li et al. (Human Immunology, Vol. 61, pp. 486-498, May 2000). Krieg teaches an immunostimulatory nucleic acid comprising at least one CpG-S motif and a nucleic acid encoding an antigen, wherein the nucleic acid further

comprises regulatory sequence for expression of DNA in eukaryotic cells and a method of using the nucleic acid to elicit an immune response in a mammalian subject (column 93-95, claims 1, 17, 18, 24, 25, and 30). Furthermore, Krieg teaches using a cell specific promoter that is operative in antigen-presenting cells (claim 25). In addition, the use of a pharmaceutically composition can be inferred, as it would otherwise be impossible to deliver the polynucleotide sequence to a subject. However, Krieg did not teach explicitly that antigen presenting cell specific promoter is a co-stimulatory promoter obtained from a CD80 or CD86 gene.

However, at the time the invention was made, Ellis teaches that CD80 and CD86 genes are expressed only in antigen presenting cells (APCs) (abstract). Li teaches that the characterization of 5'-regulatroy region (promoter region) of the human CD86 gene, which is expressed only in APCs (abstract and page 487). Zhang teaches that the CD80 promoter is expressed only in APCs (abstract).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the inventions was made to have employ either the CD80 or CD86 promoter as the APC promoter in the method of Krieg. One of ordinary skill in the art would have been motivated to use the CD80 or CD86 promoter as the APC specific promoter in the construct of Krieg to elicit an immune response in vertebrate subjects because the CD80 and CD86 genes were known to one of ordinary skill in the art to express in antigen presenting cells.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1-5 and 11-19 are rejected under 35 U.S.C 103(a) as being patentable over Krieg et al., Ellis et al., and either Zhang or Li Kuby taken with any of Gurunathan (IDS, AR-2), Pulendran (IDS, AS-2), or Wong (IDS, AP-2).

The rejections of the base claims 1 and 14 under 35 U.S.C. 103(a) are applied here as indicated above, e.g., Krieg taken with Ellis in further view of either Li or Zhang. However, Krieg taken with Ellis in further view of either Li or Zhang do not teach explicitly that the APC specific promoter is obtained from a co-stimulatory promoter obtained from CD80 or CD86 for use in a method taught by Krieg in combination with at least one cytokine selected from the group consisting of CD40L, TRANCE, or Flt-3L and administering the composition to elicit an immune response. In addition, Krieg taken with Ellis in further view of either Li or Zhang do not teach explicitly that the APC specific promoter is obtained from a co-stimulatory promoter obtained from CD80 or CD86 further comprising a nucleotide sequence encoding at least one cytokine selected from the group consisting of CD40L, TRANCE, or Flt-3 a method taught by Krieg.

However, at the time the invention was made, Gurunathan reports that CD40 ligand has a central role in the induction of both humoral and cellular immunity (abstract). In addition, Gurunathan reports that the ability of CD40L DNA to enhance a broad array of immune responses makes it a potent adjuvant for diseases requiring humoral and/or cellular immunity (pg. 4570). Pulendran shows that administration of Flt-3 ligand, a cytokine capable of inducing large numbers of dendritic cells in vivo, (a) dramatically enhances the sensitivity of antigen-specific B and T cell responses to systemic injection of a soluble protein; (b) influences the class of antibody produced; and (c) enables productive immune responses to otherwise tolerogenic

protocols (abstract). Wong reports that TRANCE enhances immune system cells by promoting the life span of mature dendritic cells (pg. 2078).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the inventions was made to combine the work of Krieg, Ellis, and either Li or Zhang taken with any of Gurunathan, Pulendran, and Wong to produce an immunogenic composition comprising either a CD80 or CD86 promoter operably linked to a polynucleotide sequence encoding at least one antigen; and using at least one cytokine selected from the group consisting of CD40L, TRANCE, and Flt-3L to elicit an immune response in a vertebrate subject. One of ordinary skill in the art would have been motivated to combine the immunogenic composition of Krieg, Ellis Li or Zhang taken with any of Gurunathan, Pulendran and Wong to enhance eliciting an immune response in subjects by assisting in regulating the development of immune effector cells (e.g. dendritic cells) as taught by Gurunathan, Pulendran and Wong.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the inventions was made to combine the work of Krieg, Ellis, and either Li or Zhang taken with any of Gurunathan, Pulendran and Wong to produce an immunogenic composition comprising either a CD80 or CD86 promoter operably linked to a polynucleotide sequence encoding at least one antigen; and one polynucleotide sequence encoding at least one cytokine selected from the group consisting of CD40L, TRANCE, and Flt-3L to elicit an immune response in a vertebrate subject. One of ordinary skill in the art would have been motivated to combine the immunogenic composition of Krieg, Ellis and either Li or Zhang taken with any of Gurunathan, Pulendran and Wong to produce the polynucleotide sequence described above, for

enhancing an immune response in subjects by assisting in regulating the development of immune effector cells (e.g. dendritic cells) as taught by Gurunathan, Pulendran and Wong.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1-5 and 9-25 are rejected under 35 U.S.C 103(a) as being unpatentable over Krieg, Ellis, and either Li or Zhang taken with any of Gurunathan, Pulendran and Wong in further view of Lai et al. (IDS, *DNA and Cell Biology*, Vol. 14(7), pp. 643-651, 1995).

The rejections of the base claims 1 and 14 under 35 U.S.C. 103(a) are applied here as indicated above, e.g., Krieg taken with Ellis in further view of either Li or Zhang, Krieg and Ellis in further view of either Li or Zhang taken with any Gurunathan, Wong, or Pulendran. Krieg taken with Ellis in further view of either Li or Zhang or Krieg and Ellis in further view of either Li or Zhang taken with any Gurunathan, Wong, or Pulendran do not teach using an immunogenic composition comprising core particle comprising a co-stimulatory promoter obtained from CD80 or CD86 gene operably linked to a polynucleotide sequence encoding at least one antigen in combination with at least one cytokine selected from the group consisting of CD40L, TRANCE, or Flt-3L in a method taught by Krieg.

However, at the time the invention was made, Lai teaches that a technique called biolistic transformation (biological ballistic system) microparticle injection, gene gun, or particle bombardment is rapid and specific for genetic immunization (abstract). The basic idea of this technique is that DNA or biological material coated onto heavy tungsten or gold particles is shot into target cells or animals (abstract). Lai expressed an antigen in a plasmid vector and introduced the vector into mice through two methods: (i) using a hand-held form of the biolistic

system that can propel DNA-coated gold microprojectiles directly into the skin; (ii) using a conventional intramuscular injection of DNA into quadricep muscles of transfected mice (abstract). Both delivery systems induced humoral and cellular immunity in the experimental mice. In addition, Lai conducted trials in mice by injecting intramuscularly (i.m.) or gene gun administration a total of four injections at 2-week intervals or a total of three injections at intervals of 2 weeks, respectively (pg. 644-45); indicating a prime and booster administration of the immunogenic composition.

It would have been *prima facie* obvious for a person of ordinary skill in the art at the time the invention was made to coat the construct of the combined cited references Krieg, Ellis and either Li or Zhang taken with any of Gurunathan, Pulendran and Wong onto heavy tungsten or gold for transdermal delivery into a vertebrate subject using a gene gun as taught by Lai. One of ordinary skill in the art would have been motivated to have employed the microparticle injection, gene gun, or particle bombardment wherein a metal particle is employed as a core carrier for delivering the immunogenic composition of the combined cited references because using a gene gun for genetic immunization saves time, money and labor, as taught by Lai.

Furthermore, it would have been obvious for a person of ordinary skill in the art to provide a prime and booster administrations of the immunogenic composition of the combine cited references to a vertebrate subject. One of ordinary skill in the art would have been motivated to have employed prime and booster administrations of the immunogenic composition in the subject because Lai teaches that the combination use of prime and booster administrations of an immunogenic composition would elicit a maximum immune response of a vertebrate subject to a targeted antigen.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
4/19/02

DAVE T. NGUYEN
PRIMARY EXAMINER